THE WALL STREET JOURNAL.
U.S. EDITION

Experimental HIV Drugs Show Promise Fighting Virus in New Ways --- Used With Other Compounds, They Could Boost Life Span Of Patients Who Are Failing

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Staff Reporters of The Wall Street Journal
1,253 words
26 February 2002
The Wall Street Journal
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English
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Corrections & Amplifications

A DRUG CANDIDATE for treating AIDS being developed by Shionogi-GlaxoSmithKline Pharmaceuticals LLC is known as S-1360. A Marketplace article and accompanying table yesterday about new AIDS drugs incorrectly gave the name of the compound as F-1360. Also, the table should have indicated that early human trials of S-1360 have begun. The table incorrectly said the compound hasn't yet been tested in humans.

(WSJ Feb. 27, 2002)

SEATTLE -- The pipeline for HIV drugs is getting fatter, adding several promising -- though still early-stage -- new compounds.

Some of these experimental drugs, unveiled yesterday at a large AIDS science meeting here called the Ninth Conference on Retroviruses and Opportunistic Infections, attack the AIDS virus in new ways. Used in combination with older generations of drugs or with each other, they could give years of life to patients who are failing on current regimens.

More Americans will need such drugs. The Centers for Disease Control released new statistics at the meeting showing that the number of Americans living with HIV increased by about 50,000 people between 1998 and 2000, largely because the anti-HIV cocktails have prevented many patients from dying.

Between 850,000 and 950,000 people in the U.S. are infected with HIV. But the CDC found that at least 42% of them are either undiagnosed or untreated, and that blacks, Latinos, drug users and heterosexuals are the most likely to be treated late. Another CDC study found that patients who delay treatment until they have full-blown AIDS have much higher death rates. Since the beginning of the epidemic, more than 457,000 Americans have died of AIDS.

While existing drugs have slashed the AIDS death rate, HIV can mutate into drug-resistant strains, and the medicines can cause severe side effects. So patients are caught in a race between the virus and the scientific search for new drugs. The experimental compounds reported yesterday include:

-- Two new "entry inhibitor" compounds that prevent the virus from entering cells.

-- Two second-generation drugs called NNRTIs, which appear to work against some viral strains that have become resistant to earlier-generation drugs in this class.

-- A compound that attacks an enzyme of HIV called integrase, which is essential for the virus to produce more copies of itself. No licensed drugs currently target this enzyme.

Researchers began exploring the potential of entry-inhibitor drugs in the mid-1990s, when they found that some people weren't infected with HIV despite multiple exposures to the virus. Some of these people have inherited a variant of a protein called CCR5 that sits on the surface of their cells. In order to infect a cell, HIV must bind to CCR5. But HIV can't bind to the CCR5 variant so it is blocked from entering the target cells.

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When this discovery was made in 1996, several drug companies raced to develop a compound that could mimic this fortuitous mutation by itself binding to the CCR5. Schering-Plough Corp. of Madison, N.J., presented the first evidence of a CCR5 blocker tested in people. While the drug, called SCH-C, was tested in only a dozen HIV-infected subjects, the new report "shows for the first time in people that blocking CCR5 is an important strategy to pursue for drug makers," said John Moore, a microbiologist at Cornell University's Weill School of Medicine, New York, one of several scientists involved in identifying the protein's role in HIV.

In the study, reported by Mark McLaughlin, a Schering-Plough researcher, SCH-C used alone over 10 days sharply reduced levels of HIV in test subjects' bloodstreams. Schering-Plough is planning to conduct similar small tests using higher doses. Dr. McLaughlin said the company is concerned about a potential side effect of the drug on heart rhythms and is seeking the highest dose it can use that doesn't cause the problem, which was seen at very high doses in an earlier trial involving healthy volunteers.

Dr. McLaughlin said the company has another drug, SCH-D, further back in the pipeline, and Pfizer Inc. is working on a CCR5 blocker but has yet to test it in patients.

While the Schering-Plough entry inhibitor blocks a human protein, Bristol-Myers Squibb Co. has developed a compound that targets an HIV protein called gp120, whose function is to latch onto cells. Bristol-Myers's molecule gets into this protein and stops it from fusing with cells.

For Richard Colonno, head of infectious-disease drug discovery at Bristol-Myers, the compound represents vindication. He rankles at criticism in the industry that Bristol-Myers isn't good at discovering drugs, saying, "I take it very personally." About 30 Bristol-Myers scientists have been working on the project.

The compound hasn't been tested in humans, and Dr. Colonno declined to say when clinical trials might start.

Meeting organizers highlighted an experimental drug made by a small Belgian company, Tibotec-Virco NV, that is in a class of medicines called NNRTIs. Patients often prefer drugs in this class because the drugs usually don't cause the strange, sometimes disfiguring and occasionally life-threatening alterations in fat deposits and cholesterol that other AIDS drugs can cause.

In patients infected with strains of HIV resistant to first-generation NNRTIs, the Tibotec drug alone sharply suppressed the amount of HIV in the bloodstream in just one week. In patients whose virus wasn't resistant, the Tibotec compound, called TMC125, looked as powerful as five older drugs taken in combination, according to a second small study. TMC125 has "amazing potency," said Joep Lange, a veteran HIV researcher at the University of Amsterdam who conducted the second study.

Tibotec-Virco is planning larger clinical trials and hopes to file for regulatory approval as early as 2004.

Bristol-Myers also has a second-generation NNRTI that it acquired when it bought the pharmaceutical unit of DuPont Co. in October 2001. A study of this experimental drug, called DPC 083, suggested it, too, could work against some drug-resistant strains of HIV.

Finally, researchers from Shionogi & Co. of Japan unveiled a compound that targets an entirely different part of HIV, an enzyme called integrase that is essential for the virus to make new copies of itself. The integrase-inhibitor compound, called F-1360, will be developed together with GlaxoSmithKline PLC through a 50-50 joint venture called Shionogi-GlaxoSmithKline Pharmaceutical Co. Researchers have long felt that integrase would make an excellent drug target. Merck & Co. has also developed an experimental integrase inhibitor and plans to initiate Phase I human trials next month.

Expanding the Pipeline

Some HIV drugs currently in developmentCompany Drug Testing stage

Company: Shionogi-GlaxoSmithKline

Drug: F-1360 Integrase inhibitor

Testing Stage: Not yet tested in humans

Company: Merck & Co.

Drug: Integrase inhibitor

Testing Stage: About to be tested in small human safety trials

Company: Tibotec-Virco

Drug: TMC125 NNRTI

Testing Stage: Small clinical trials

Company: Bristol-Myers Squibb

Drug: BMS 806 Entry Inhibitor; DPC 083 NNRTI

Testing Stage: Not yet tested in humans; Phase II clinical trials

Company: Pfizer

Drug: CCR5 blocker Entry Inhibitor

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Testing Stage: Not yet tested in humans
Company: Schering-Plough
Drug: SCH-C CCR5 blocker Entry inhibitor
Testing Stage: Tested in only a dozen HIV-infected subjects

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